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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,834	11/21/2003	Margot O'Toole	WYE-014	3669

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/718,834	O'TOOLE ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 29-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/29/2005 01/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of claims 9-28 in the reply filed on 07/13/2006 is acknowledged. Claims 1-8 and 29-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/13/2006. The amendments of 07/13/2006 have been entered in full. Claims 9-28 are under examination.

Specification

2. The disclosure is objected to because of the following informalities: Amino acid sequences in the Description are inconsistent with the Sequence Listing.

a. SEQ ID NO:15 is described on page 66 as differing from SEQ ID NO:2 at a single residue in position 1139. The Sequence Listing shows SEQ ID NO:15 as having only 160 amino acids.

b. SEQ ID NO:20 is listed in Table 4 (page 8) as being gi|20849521|, which is identified in Table 3 as being a *Mus musculus* protein similar to human KIAA1698. The Sequence listing shows SEQ ID NO:20 as an *Anopheles gambiae* protein.

c. SEQ ID NO:21 is listed in Table 4 (page 8) as being gi|21296297|, which is identified in Table 3 as being an *Anopheles gambiae* protein. The Sequence listing shows SEQ ID NO:21 as a human peptide of 27 amino acids.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 20-24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 20 is drawn to a polypeptide comprising at least five contiguous amino acids of SEQ ID NO:15. By failing to specify any human input or activity, the claim reads on a polypeptide as it exists in nature. Products of nature do not constitute patentable subject matter. This rejection may be obviated by recitation of an *isolated* polypeptide.

5. Claims 9-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

6. The claims are drawn to a genus of proteins, fusion proteins, and compositions comprising domains with various degrees of identity with the amino acid sequence of SEQ ID NO:2 or SEQ ID NO: 15, collectively referred to as BFLP1698 polypeptides. The specification generally asserts several utilities for BFLP1698 polypeptides: as an indicator of the presence of or predisposition to lupus nephritis in a subject (claim 41 and [007]); a target for identifying agents that, like rapamycin, are useful in treating symptoms of lupus nephritis ([005] and claim 43); treating lupus nephritis in a subject by administering an agent that inhibits activity of a BFLP1698 polypeptide (claim 49). (**NB**. Citations refer to the specification as it appears in U.S. Patent Application Publication 20050119208). These asserted utilities are credible to the extent

that it is within the realm of possibility that the BFLP1698 polypeptide could be used for these purposes. The asserted utilities are specific in the sense that they rely on properties imputed to the BFLP1698 polypeptide (specific expression and/or a role in the pathology of lupus nephritis) that are not shared by all proteins. However, none of the asserted utilities are substantial, because in fact, the disclosure does not teach any relationship of the BFLP1698 protein to lupus nephritis or any other disease.

7. The specification states at [0023] that BFLP1698 "Gene expression is elevated in mice with lupus nephritis, and is lower in mice that have been successfully treated with rapamycin or anti-B7 antibodies." This conclusion is supported by the data in Figure 1, which shows mRNA levels as assessed by hybridization of cDNA to an oligonucleotide array (Example 1). The specification states at [0005], however, that, "the expression level of the gene does not decrease markedly in response to treatment with rapamycin", which clearly contradicts the data in Figure 1. To resolve the conflict, one of skill in the art might suppose that "expression level of the gene" is meant as "expression level of the polypeptide encoded by the gene" in [0005]. This interpretation is not supported by any data and is never even clearly stated anywhere in the disclosure. The envisioned scenario would have the BFLP1698 polypeptide specifically expressed highly during the disease state, and then remaining high despite declining mRNA expression after rapamycin treatment. Such discordant mRNA and protein expression is possible, but in the absence of a direct measurement of protein expression, one of skill in the art would have reason to doubt the assertion that the expression of any particular protein remains high while its mRNA declines.

8. Furthermore, while the specification shows that BFLP1698 mRNA levels correlate with

disease state, it does not show that the same is true for the BFLP1698 polypeptide. The expectation that increased mRNA levels are predictive of corresponding increased levels of the encoded protein is not supported by studies aimed directly to the relationship of mRNA to polypeptide levels. Chen *et al.* (Molecular & Cellular Proteomics 1.4 pp. 304-313, 2002) found a statistically significant correlation between mRNA and protein levels in only 28 of 165 polypeptides (17%) or 21 of 98 genes (21.4%) expressed in lung adenocarcinomas (see Abstract). No significant correlation between mRNA and protein levels was found if average levels were applied across the whole data set of 165 polypeptides expressed from 98 genes (Abstract). Chen *et al.* further state, "The use of mRNA expression levels by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation my influence the level of a protein present in a given cell or tissue." (p.304, right column). Greenbaum *et al.*, (Genome Biology 4:117; 2003) reviewed the published work and concluded that most studies found weak or no significant relationships correlation between mRNA and protein levels (paragraph bridging pp. 1173-1174). Greenbaum *et al.* studied over 2000 ORFs for which polypeptide abundances had been determined by various means. They found that the correlation between mRNA and protein may be high or low, depending on factors such as codon usage, variability of expression (see Figure 2), and subcellular localization (p1117, right column). It should be noted here that the instant specification provides no data for these factors.

9. Thus, the art indicates that polypeptide levels cannot be predicted from transcript levels. Therefore the instant disclosure does not substantiate any of the asserted utilities for BFLP1698

polypeptides.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 9-28 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Furthermore, even if the utilities asserted for BFLP1698 polypeptides were deemed to be substantial, the specification clearly does not enable one skilled in the art to use BFLP1698 polypeptides. As noted, the art indicates that polypeptide levels cannot be predicted from transcript levels. Therefore, BFLP1698 polypeptides are not enabled as markers because it is not known whether BFLP1698 polypeptides are specifically highly expressed in disease. BFLP1698 polypeptides are not enabled as therapeutic targets because no role for BFLP1698 polypeptides in pathology has been established. The specification puts forth a hypothesis that BFLP1698 polypeptides bind rapamycin, but does not provide any example or evidence that BFLP1698 polypeptides are targets for any known therapeutic agent. The courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable

members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997).

12. Claims 9-12 and 15-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of proteins comprising domains with various degrees of identity with the amino acid sequence of SEQ ID NO:2 or SEQ ID NO: 15 (which differ from one another by a single amino acid). To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In claims 9, 11, 12, 15, and 16 in this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. Claims 18 and 20-24 require only conservation of any five contiguous amino acids from a reference sequence. There is no identification of any particular portion of the structure that must be conserved. The nearly limitless number of encompassed polypeptides is not substantially reduced by the size limitations in claims 18 and 22-24, nor by the exclusion of a single sequence (SEQ ID NO:21) in claim 18. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

13. Claim 10 recites a functional limitation wherein the polypeptide binds rapamycin; claims 17, 19, 21, and 25-28, recite a rapamycin-binding domain. The specification does not describe or disclose any protein that binds rapamycin or has a rapamycin-binding domain. The basis for this limitation is "the discovery of a gene, named BFLP1698, whose expression is increased in kidney tissue in mice with lupus nephritis; however, the expression level of the gene does not decrease markedly in response to treatment with rapamycin" [0005]. According to the specification, "This expression profile indicates that the product of the BFLP1698 gene interacts with rapamycin when this antibiotic is administered to ameliorate the symptoms of lupus nephritis. In the absence of rapamycin, the gene product is free to bring about the diseased state, and its effects can include the activation of genes required to bring about the diseased state. In the presence of rapamycin, the BFLP1698 gene product is inactive and the disease state diminishes" [0005]. This conclusion, however, is a highly speculative working hypothesis. The putative interaction between the BFLP1698 and rapamycin need not be by direct binding; the actual target of rapamycin could be an upstream activator or downstream effector in a pathway involving the BFLP1698 gene product. Furthermore, the underlying observation is contradicted at [0023], "Gene expression is elevated in mice with lupus nephritis, and is lower in mice that have been successfully treated with rapamycin or anti-B7 antibodies." Therefore, BFLP1698 gene expression may or may not be controlled by rapamycin. The BFLP1698 gene product may be expressed in antigen-presenting cells (hence expression is lowered by anti-B7) but this expression may or may not be a cause of any pathological process. Clearly, the specification does not convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of a protein that binds rapamycin.

14. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

15. With the exceptions of SEQ ID NO: 2 and SE ID NO:15, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

16. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

17. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 18-24 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 2004030615, filed September 29, 2003, with priority from U.S. Provisional Application 60/414971 (October 2, 2002). The amino acid sequence of SEQ ID NO: 3235 of WO 2004030615, comprises 993 amino acids (27 to 1019, inclusive) and differs from the corresponding region of SEQ ID NO:2 by one conservative substitution. [Search results are available in SCORE. For convenience, an alignment is appended to this office action.] Therefore, SEQ ID NO:3235 meets all of the length limitations of claims 18 and 22-24, comprises at least five contiguous amino acids of SEQ ID NO:2 (as in claim 18) or SEQ ID NO:15 (as in claim 20), and further comprises an amino acid sequence other than SEQ ID NO:21 (claim 18). If indeed SEQ ID NO: 2 comprises a rapamycin-binding domain, SEQ ID NO: 3235 of WO 2004030615 inherently comprises one also, absent evidence to the contrary; thus claims 19 and 21 are anticipated.

20. Claims 20, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 200259260 A2, published August 1, 2002, with priority from November 17, 2000. The claims are drawn to a polypeptide comprising at least five contiguous amino acids of SEQ ID NO:15.

Claims 22 and 23 specify that the polypeptide is at least 50 and 100 amino acids in length, respectively. The amino acid sequence of SEQ ID NO: 521 from WO 200259260 (Cite No. C1 on IDS filed January 30, 2005) is 131 amino acids in length and the first 50 amino acids are identical to the first 50 amino acids of SEQ ID NO:15. If indeed SEQ ID NO: 15 comprises a rapamycin-binding domain, SEQ ID NO: 521 from WO 200259260 inherently comprises one also, absent evidence to the contrary; thus claim 21 is anticipated.

Conclusion

21. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
27 September 2006

DAVID S. ROMEO
PRIMARY EXAMINER